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(71) Applicant: BAKER NORTON PHARMACEUTICALS, INC. [US/US]; 4400 Biscayne Boulevard, Miami, FL 33137 (US).		
(72) Inventors: BLONDINO, Frank, E.; 6237 Rose Terrace, Plantation, FL 33317 (US). BRUCATO, Michael; 9801 N.W. 1st Avenue, Miami Shores, FL 33150 (US). BUENAFE, Maria, W.; 110 Southshore Drive #3-C, Miami Beach, FL 33141 (US). CAVANAUGH, Kelly, A.; 27421 S.W. 154th Avenue, Homestead, FL 33032 (US). MEDINA, Raul, A.; 2694 N.W. 99th Place, Miami, FL 33172 (US).		<b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(74) Agents: LEVI-MINZI, Simona, A. et al.; Baker Norton Pharmaceuticals, Inc., 4400 Biscayne Boulevard, Miami, FL 33137 (US).		
(54) Title: PHARMACEUTICAL AEROSOL FORMULATIONS CONTAINING FLUOROALKANES AND BUDESONIDE		
(57) Abstract		
Provided is a solution aerosol formulation adapted for use in a pressurized aerosol container. The aerosol formulation is formulated from a composition containing Budesonide, at least one fluoroalkane propellant, and a cosolvent present in an amount that dissolves or solubilizes the Budesonide in the mixture of cosolvent and propellant.		

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## PHARMACEUTICAL AEROSOL FORMULATIONS CONTAINING FLUOROALKANES AND BUDESONIDE

### 1. Field of the Invention.

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The invention relates to pharmaceutical aerosol formulations containing Budesonide dissolved or solubilized in a fluoroalkane(s) and a cosolvent(s).

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### 2. Background of the Invention.

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Chlorohydrocarbon and chlorofluorocarbon propellants used in medical aerosol formulations are generally considered to be environmentally unfriendly. Therefore, these propellants have been largely replaced by hydrofluoroalkanes such as 1,1,1,2 tetrafluoroethane ("HFA-134a") and 1,1,1,2,3,3,3 heptafluoropropane ("HFA-227ea") that have been identified as safe for use in pressurized metered dose inhalers.

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Medicinal aerosol formulations are generally of the solution or suspension type. Each type is composed of at least the medicament and the propellant. The solution type aerosol formulation contains the medicament dissolved or solubilized in the propellant, or a mixture of propellant and cosolvent. The suspension type aerosol formulation contains the medicament in the form of particles which are dispersed in the propellant. The suspension type aerosol formulations usually contains a surfactant, and can also include a cosolvent. Conventional Budesonide aerosol formulations are of the suspension type.

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U.S. Patent No. 5,736,124 (Akehurst) discloses a suspension type aerosol formulation in which the medicament is in the form of particles dispersed in a cosolvent. The cosolvent is present in an amount less than 5% by weight to avoid dissolving the medicament (column 4, lines 13-24).

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Published International Application No. WO 98/05302 discloses a suspension type aerosol formulation in which the medicament is in the form of particles dispersed in a cosolvent. The cosolvent can be present in amount of from 6 to 25% by weight. However, WO 98/05302 teaches that the medicament and cosolvent selected should be such that the

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medicament is not dissolved in the cosolvent and the particulate shape of the medicament is retained.

The drug Budesonide has proven difficult to formulate in conventional aerosols. There remains, therefore, an important need for aerosol formulations containing Budesonide that remain chemically and physically stable during storage at ambient conditions of temperature and humidity.

### SUMMARY OF THE INVENTION

An objective of the present invention is to provide a pressurized metered dose inhaler containing a stable solution formulation of Budesonide which does not require the use of refrigeration.

Another objective of the present invention is to provide a stable solution formulation of Budesonide that is suitable for use as an aerosol, which does not require the use of refrigeration.

The above objectives and other objectives are surprisingly achieved by the following. The present invention provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

Budesonide;  
at least one fluoroalkane propellant; and  
a cosolvent present in an amount that dissolves or solubilizes the Budesonide in the mixture of cosolvent and propellant.

The present invention also provides a novel solution aerosol formulation adapted for use in a pressurized aerosol container. The aerosol formulation is formulated from a composition comprising:

Budesonide;  
at least one fluoroalkane propellant; and  
a cosolvent present in an amount that dissolves or solubilizes the Budesonide in the mixture of cosolvent and propellant.

### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

It has been unexpectedly discovered that chemically and physically

stable aerosol formulations of Budesonide can be formulated utilizing unusually high concentrations of cosolvent in which the Budesonide is dissolved or solubilized in the mixture of cosolvent and propellant. Budesonide aerosol formulations can be formed according to the present invention which exhibit stability under elevated temperatures (40°C), thus requiring no refrigeration.

The amount of Budesonide utilized in the present solution type aerosol formulations is usually from about 0.01 to about 1% by weight, preferably about 0.05 to about 0.5 % by weight, and most preferably about 0.3% by weight, based on the total weight of the aerosol formulation. All weight percents herein are based on the total weight of the formulation unless stated otherwise.

Any cosolvent that is suitable for inhalation and capable of dissolving or solubilizing the Budesonide in the mixture of cosolvent and propellant can be used. Examples of suitable cosolvents include alcohols, ethers, hydrocarbons, and perfluorocarbons. Preferably, the cosolvent is a short chain polar alcohol. More preferably, the cosolvent is an aliphatic alcohol having from one to six carbon atoms, such as ethanol or isopropanol. The most preferred cosolvent is ethanol. Examples of suitable hydrocarbons include n-butane, isobutane, pentane, neopentane and isopentanes. Examples of suitable ethers include dimethyl ether and diethyl ether. Examples of suitable perfluorocarbons include perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane.

When ethanol is utilized as the cosolvent, the cosolvent is usually present in an amount of from about 6% to about 40% by weight, based on the total weight of the aerosol formulation. The ethanol should be present in an amount which fully dissolves or solubilizes the Budesonide in the mixture of ethanol and propellant. Preferably, ethanol is present in amount sufficient to fully maintain the Budesonide in solution at freezing temperatures, such as 0°C. In general, as the temperature is decreased, the solubility of Budesonide in ethanol is decreased. Therefore, an excess of ethanol over the amount required to fully dissolve or solubilize the Budesonide at ambient or room temperature is preferred. In this regard, ethanol is preferably present in an amount of at least 10% by weight, more preferably at least 15% by weight, even more preferably

at least 20% by weight, and most preferably at least 25% by weight. Based on the disclosure provided herein, one skilled in the art will recognize that lower concentrations of medicament usually require lower concentrations of cosolvent, and vice versa, in order to form a stable solution. Furthermore, one skilled in the art will recognize that the type of propellant utilized can also affect the amount of ethanol required to fully dissolve or solubilize the Budesonide in the mixture of ethanol and propellant. In general, the greater the polarity of the propellant the less ethanol required to fully dissolve or solubilize the Budesonide. For example, when HFA-134a is utilized as the propellant, the amount of ethanol is preferably from about 10 to about 30% by weight. When HFA-227ea is utilized as the propellant, the amount of ethanol is preferably from about 6 to about 20% by weight.

Any fluoroalkane propellant that is suitable for inhalation can be used. Examples of suitable fluoroalkanes include HFA-134a, HFA-227ea, HFA-125 (pentafluoroethane), HFA-152a (1,1-difluoroethane), and HFA-32 (difluoromethane). Hydrocarbon and/or aliphatic gases may be added to modify propellant characteristics as required. Preferably, the aerosol formulation is substantially free of chlorofluorocarbons. However, if desired chlorofluorocarbons can be utilized. Preferably, the fluoroalkane is 1,1,1,2-tetrafluoroethane (HFA-134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA-227ea). Most preferably, only a single fluoroalkane is utilized as the propellant.

The propellant is usually present in an amount of from about 60% to about 94% by weight, preferably from about 70 to about 90% by weight, based on the total weight of the aerosol formulation.

A preferred aerosol formulation comprises HFA-134a or HFA-227ea in an amount less than about 90% by weight, ethanol in an amount of at least about 10% by weight, and Budesonide in an amount of from about 0.05 to about 0.5% by weight. A particularly preferred aerosol formulation comprises about 86% by weight of HFA-227ea, about 14% by weight of ethanol, and about 0.3% by weight of Budesonide. Another particularly preferred aerosol formulation comprises about 75% by weight of HFA-134a, about 25% by weight of ethanol, and about 0.3% by weight of Budesonide.

The aerosol formulation is preferably free of surfactants.

Pressurized metered dose inhalers are now well known in the art. Any pressurized metered dose inhaler that is suitable for application of medicaments to the lungs or nose of a patient can be used. Pressurized metered dose inhalers usually are equipped with an actuator having a spray orifice diameter of about 460 $\mu$ m. However, with the higher concentrations of solvent employed in the present invention, it may be desirable that the solvent evaporates as soon as possible after inhalation. This can be achieved by reducing particle size by reducing the spray orifice diameter, for example, to 250 $\mu$ m, in combination with using solvent concentrations greater than about 10% by weight. Based on the disclosure provided herein, one skilled in the art will be able to adjust the component composition to deliver a desired dose for the selected metered valve, without undue experimentation. For example, the composition may be altered to adjust the vapor pressure of the formulation. The aerosol formulation and metering valve are usually selected to provide a therapeutically effective amount of the Budesonide per activation. An example of a therapeutically effective amount of Budesonide is about 50 to about 400  $\mu$ g per activation, preferably about 150 to about 250  $\mu$ g per activation.

The pressurized metered dose inhaler can be formed by any suitable method. For example, the selected amount of Budesonide can be weighed and inserted into a suitable container, such as a plastic coated glass bottle or aluminum canister. The cosolvent can then be weighed and added to the container. Once all of the non-gaseous components have been added to the container, the metered valve can be crimped on to seal the container. Then, the desired amount of propellant can be added to the container through the metered valve. The Budesonide can be dissolved or solubilized into the mixture of cosolvent and propellant by agitating the formulation, such as by sonication. About 5 minutes of sonication has been found to be suitable to dissolve or solubilize a formulation having a total weight of about 12 grams.

The present invention will now be explained with reference to the following non-limiting examples.

35           **Examples 1- 4**

Four solution aerosols compositions according to the present invention were formulated by combining the components shown in Tables I and V, using the following steps:

- 5 1. Weighing the cosolvent into a plastic coated glass bottle or an aluminum canister.
2. Adding the weighed medicament to the bottle or canister.
3. Crimping a valve upon the bottle or canister.
4. Adding a known amount of propellant through the valve into the bottle or canister.
- 10 5. Sonicating the formulation for about 5 minutes.

The formulations were tested using the following three very well known testing methods and the Pharmacopeia Forum, vol. 22, no. 6 standards:

- 15 (1) Andersen Multistage Cascade Impactor;
- (2) Single Stage Liquid Impinger; and
- (3) Unit Spray.

Table II discloses the test results of the Example 1 formulation using the Andersen Multistage Cascade Impactor. These test results demonstrate that the solution formulation according to the present invention is suitable for application to the lungs. The stages 2 through F represent medicament that is capable of reaching the lungs from a conventional applicator. A total medicament amount of about 30% for stages 2 through F is considered good. As can be seen from Table II, the present invention achieved a high total amount of 46.99% for the stages 2 through F.

Table III discloses the test results of the Examples 1 and 2 formulations using a Single Stage Impinger. Stage 2 represents medicament that is capable of reaching the lungs from a conventional applicator. A medicament amount of about 30% for stage 2 is considered good. As can be seen from Table III, the present invention is capable of achieving a remarkably high total amount of up to 63.47%.

Table IV discloses the test results of the Example 1 formulation using a Unit Spray Analysis. This test demonstrates that about 10% of

the medicament was retained on the actuator and about 90% of the medicament was dispensed to the dose tube, which represents that the composition is acceptable for use as an aerosol formulation.

Table VI discloses the test results of the Examples 3 and 4 formulations using a Unit Spray Analysis, in which the formulations were stored in an oven at 40°C for 5 days. The test results in Table VI demonstrate that the Budesonide aerosol formulations according to the present invention are remarkably stable at elevated temperatures and therefore do not require refrigeration. The test results also demonstrate that about 10% of the medicament was retained on the actuator and about 90% of the medicament was dispensed to the dose tube, which represents that the composition is acceptable for use as an aerosol formulation.

Table VII discloses the test results of the Example 3 formulation using an Andersen Multistage Cascade Impactor. The beginning, middle and end of the can each exhibited a total amount of medicament in the stages 2 through F which was acceptable for application to the lungs. The beginning had a total amount of 37.35%, the middle had a total amount of 36.54%, and the end of the can had a total amount of 30.56%, for the stages 2 through F.

Table I

Component	Example 1		Example 2	
	(g)	(%)	(g)	(%)
Budesonide	0.0361	0.282%	0.0361	0.288%
Ethanol	1.76	13.74%	1.50	12.01%
HFA-227ea	11.0220	85.98%	10.9815	87.70%

Table II

	Example 1	
	( $\text{mg}$ )	(%)
Actuator	106.07	6.36
Valve	7.11	0.43
Induction port	609.32	36.52
Stage 0	111.80	6.70
Stage 1	50.45	3.02
Stage 2	18.97	1.14
Stage 3	62.66	3.76
Stage 4	205.02	12.29
Stage 5	314.00	18.82
Stage 6	93.27	5.59
Stage 7	37.11	2.22
Stage F	52.82	3.17
Total Drug	1668.58	100
No Shots	10	
Avg. Shot Weight	57.92	
Actual Dose Delivered ( $\text{mg}/\text{actuation}$ )	166.86	
Material Balance (%)	102	
MMAD (microns)	2.1	
GSD	2.3	
Fine particle Dose ( $\text{mg}$ )	784	
Fine Particle Fraction (%)	50%	

Table III

	Example 1		Example 2			
	Amt ( $\mu$ g)	Amt (%)	Amt ( $\mu$ g)	Amt (%)	Amt ( $\mu$ g)	Amt (%)
Valve/Actuator	47.59	12.25	193.92	68.04	21.97	8
Throat/Neck	87.33	22.47	25.11	8.81	60.38	21.98
Stage 1 (Upper Impinger)	25.09	6.46	5.01	1.76	17.99	6.55
Stage 2 (Lower Impinger)	228.56	58.82	60.95	21.36	174.35	63.47
No. Of Shots	2		2		2	
Avg. Shot Weight	63.55		47.25*		63.05	
Actual Dose Delivered	194.28		142.50		137.35	
Material Balance (%)	109		105		76	

\* possible actuation misfire

Table IV

	Example 1	
	Amt. ( $\mu$ g)	Amt. (%)
Actuator	41.08	11.17
Dose Tube	326.63	88.93
No. Of Shots	2	
Avg. Shot Weight	60.95	
Actual Dose Delivered	183.86	
Material Balance (%)	107.12	

Table V

	Example 3		Example 4	
	Component	grams	%	grams
Budesonide	0.0319	0.25%	0.0322	0.26%
Ethanol	2.5000	19.21%	2.5344	20.21%
HFA-134a	10.4817	80.54%	9.9748	79.53%

Table VI

	Example 3 (Aged)						Example 4 (Aged)	
	Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Test 1	Test 2
Amt. On Actuator ( $\mu$ g)	32.32	41.62	51.52	42.84	48.70	50.51	54.87	50.11
% Amt. (Actuator)	13.96	10.44	13.24	10.98	12.78	13.08	14.85	13.11
Amt. In Tube ( $\mu$ g)	199.29	356.90	337.48	347.43	332.31	332.52	314.62	332.28
% Amt. (Tube)	86.04	89.56	86.76	89.02	87.22	86.92	85.15	86.89
No. Of Shots	2	2	2	2	2	2	2	2
Avg. Shot Weight	44.80	74.35	72.95	74.15	72.05	72.55	69.6	70.8
Dose Delivered ( $\mu$ g)/Actuation	115.81	199.26	194.50	195.13	190.50	193.02	184.74	181.72
Avg. Material Balance	106%	109%	109%	107%	108%	109%	103%	105%

Table VII

	Example 3					
	(Beginning)		(Middle)		(End)	
	Amt. ( $\mu$ g)	Amt. (%)	Amt. ( $\mu$ g)	Amt. (%)	Amt. ( $\mu$ g)	Amt. (%)
Actuator	127.1	7.72	111.23	6.38	144.95	7.96
Valve	0.0	0.0	0.0	0.0	0.0	0.0
Induction Port	784.96	47.69	870.78	49.91	998.48	54.83
Stage 0	88.70	5.39	93.77	5.37	84.62	4.65
Stage 1	30.47	1.85	31.28	1.79	36.36	2.00
Stage 2	0.00	0.0	0.00	0.0	0.00	0.0
Stage 3	27.70	1.68	29.53	1.69	0.00	0.00
Stage 4	116.81	7.10	124.53	7.14	87.07	4.78
Stage 5	263.08	15.98	273.07	15.65	249.01	13.67
Stage 6	102.60	6.23	101.21	5.80	108.12	5.94
Stage 7	48.37	2.94	50.46	2.89	52.67	2.89
Stage F	56.30	3.42	58.71	3.37	59.81	3.28
Total Drug	1646.09	100.00	1744.56	100.00	1821.09	100.00
No Shots	10		10		10	
Avg. Shot Weight	73.03		72.63		71.66	
Actual Dose Delivered ( $\mu$ g/actuat.)	164.60		174.46		182.11	
Material Balance (%)	92%		98%		104%	
MMAD (microns)	1.8		1.8		1.7	
GSD	2.6		2.6		2.7	
Fine Particle Dose ( $\mu$ g)	615		638		557	
Fine Particle Fraction (%)	40%		39%		33%	

While the claimed invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one of ordinary skill in the art that various changes and modifications can be made to the claimed invention without departing from the spirit and scope thereof.

**CLAIMS:**

1. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

Budesonide;

at least one fluoroalkane propellant; and  
a cosolvent present in an amount that dissolves or  
solubilizes said Budesonide in the mixture of cosolvent and  
propellant.

2. A pressurized metered dose inhaler according to claim 1, wherein  
said cosolvent comprises ethanol.

3. A pressurized metered dose inhaler according to claim 2, wherein  
said ethanol is present in an amount of at least 10% by weight.

4. A pressurized metered dose inhaler according to claim 2, wherein  
said ethanol is present in an amount of at least 15% by weight.

5. A pressurized metered dose inhaler according to claim 2, wherein  
said ethanol is present in an amount of at least 20% by weight.

6. A pressurized metered dose inhaler according to claim 2, wherein  
said ethanol is present in an amount of at least 25% by weight.

7. A pressurized metered dose inhaler according to claim 1, wherein  
said formulation is free of a surfactant.

8. A pressurized metered dose inhaler according to claim 1, wherein  
said propellant comprises 1,1,1,2-tetrafluoroethane or  
1,1,1,2,3,3-heptafluoropropane.

9. A pressurized metered dose inhaler according to claim 1, wherein said Budesonide is present in an amount of from about 0.01 to about 1% by weight, based on the total weight of the composition.
- 5 10. A pressurized metered dose inhaler according to claim 1, wherein said formulation is substantially free of chlorofluorocarbons.
- 10 11. A pressurized metered dose inhaler according to claim 1, wherein said propellant is present in an amount of from about 70 to about 94% by weight.
12. A pressurized metered dose inhaler according to claim 1, wherein said cosolvent comprises an aliphatic alcohol having from 1 to about 6 carbon atoms.
- 15 13. A pressurized metered dose inhaler according to claim 1, wherein said cosolvent is present in an amount sufficient to maintain said Budesonide in solution at 0°C.
- 20 14. A pressurized metered dose inhaler according to claim 1, wherein said Budesonide is present in an amount of about 0.05 to about 0.5% by weight, said cosolvent comprises ethanol in an amount of about 10 to about 40% by weight, and said propellant is present in an amount of from about 60% to about 90% by weight, all weights based on the total weight of said aerosol formulation.
- 25 15. A pressurized metered dose inhaler according to claim 1, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

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16. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

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Budesonide;

1,1,1,2-tetrafluoroethane as a propellant; and  
at least about 10% ethanol, wherein the ethanol is present  
in an amount that dissolves or solubilizes said Budesonide  
in the mixture of 1,1,1,2-tetrafluoroethane and propellant.

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17. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

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Budesonide;

1,1,1,2,3,3-heptafluoropropene as a propellant; and  
at least about 10% ethanol, wherein the ethanol is present  
in an amount that dissolves or solubilizes said Budesonide  
in the mixture of 1,1,1,2,3,3-heptafluoropropene and  
propellant.

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18. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

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Budesonide;

at least one fluoroalkane propellant; and  
a cosolvent present in an amount that dissolves or  
solubilizes said Budesonide in the mixture of cosolvent and  
propellant.

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19. A solution aerosol formulation according to claim 18, wherein said cosolvent comprises ethanol.

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20. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 10% by weight.

21. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 15% by weight.
22. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 20% by weight.  
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23. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 25% by weight.
24. A solution aerosol formulation according to claim 18, wherein said formulation is free of a surfactant.  
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25. A solution aerosol formulation according to claim 18, wherein said propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.  
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26. A solution aerosol formulation according to claim 18, wherein said Budesonide is present in an amount of from about 0.01 to about 1% by weight, based on the total weight of the composition.  
20
27. A solution aerosol formulation according to claim 18, wherein said formulation is substantially free of chlorofluorocarbons.
28. A solution aerosol formulation according to claim 18, wherein said propellant is present in an amount of from about 70 to about 94% by weight.  
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29. A solution aerosol formulation according to claim 18, wherein said cosolvent is present in an amount sufficient to maintain said Budesonide in solution at 0°C.  
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30. A solution aerosol formulation according to claim 18, wherein said cosolvent comprises an aliphatic alcohol having from 1 to about 6 carbon atoms.

5           31. A solution aerosol formulation according to claim 18, wherein said Budesonide is present in an amount of about 0.05 to about 0.5 % by weight, said cosolvent comprises ethanol in an amount of about 10 to about 40% by weight, and said propellant is present in an amount of from about 60% to about 90% by weight, all weights based on the total weight of said aerosol formulation.

10          32. A solution aerosol formulation according to claim 18, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

15          33. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

20              Budesonide;  
1,1,1,2-tetrafluoroethane as a propellant; and  
at least about 10% ethanol, wherein the ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of 1,1,1,2-tetrafluoroethane and propellant.

25          34. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

30              Budesonide;  
1,1,1,2,3,3-heptafluoropropane as a propellant; and  
at least about 10% ethanol, wherein the ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of 1,1,1,2,3,3-heptafluoropropane and propellant.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/30171

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K31/58 A61K9/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24420 A (BIOGLAND IRELAND) 11 June 1998 (1998-06-11) claims 1-3,10,17 page 5, line 1 - line 4	1-34
X	EP 0 504 112 A (CIBA-GEIGY) 16 September 1992 (1992-09-16)  page 8; example 23 page 3, line 3 - line 6 page 8, line 51 - line 53	1-5, 8-22, 25-34
<input type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
* Special categories of cited documents :  "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
28 April 2000	08/05/2000	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Authorized officer  Ventura Amat, A	

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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